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EXAMINER
ALONZO, NORMA LYN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	10/033,400	CHEN, PENG-SHENG	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/11/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Alonzo, whereas any inquiries relating to formal matters should be directed to Ms. Jacob, LIE. The phone numbers for Examiner Alonzo and LIE Jacob are provided at the end of this office action.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/11/04 has been entered.

3. Applicant amendment filed on 5/11/04 with an RCE request has been entered.

4. Claims 1-9 and 11-21 are pending and are under consideration.

Claim Objections

5. Claim 2 is objected to because of the following informalities: The term "NGF" is inappropriate. The full term must be spelled out with the first use, however, subsequent uses can be shortened to an acronym. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-9 and11-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a model system for artificially inducing a heart arrhythmia consisting of a canine test subject wherein the anterior descending portion of the coronary artery of the subject is surgically ligated for induction of a myocardial infarction wherein said canine test subject has coupled to a myocardial nerve conduction pathway leading to the left ventricle of the heart, means for stimulating myocardial hyperinnervation in the left ventricle comprising an electrical lead for administering an electrical current to the myocardial nerve conduction pathway or an osmotic pump for administering nerve growth factor, wherein canine test subject further comprises electrical leads coupled to the heart, means for detecting electrical heart

signals representententative of the induced heart arrhythmia comprising an implantable cardioverter-defibrillator (ICD) as a means for pacing the heart in response to the induced heart arrhythmia, wherein the ICD further applies therapies to prevent occurrence of further arrhythmias or ventricular fibrillation of the heart of the test subject, wherein the model system further comprises a telemetry system for downloading signals and any response applied by the ICD; and a test analysis system for processing the signals received from the ICD to verify efficacy of any response applied by the ICD to the heart of the canine test subject, does not reasonably provide enablement for a model system for artificially inducing a heart arrhythmia comprising any non-human test subject and wherein the atrioventricular block is produced by a chemical or combination of surgical and chemical method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make

or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 , 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses a model system for artificially inducing a heart arrhythmia comprising a non-human test subject having an artificially induced atrioventricular block in the heart, wherein the anterior descending portion of the coronary artery of the heart is surgically or chemically blocked, or both, wherein said canine test subject has coupled to a myocardial nerve conduction pathway leading to the left ventricle of the heart, means for stimulating myocardial hyperinnervation in the left ventricle comprising an electrical lead for administering an electrical current to the myocardial nerve conduction pathway or an osmotic pump for administering nerve growth factor , wherein canine test subject further having electrical leads coupled to the heart, means for detecting electrical heart signals represententative of the induced heart arrhythmia comprising an implantable cardioverter-defibrillator (ICD) as a means for pacing the heart in response to the induced heart arrhythmia, wherein the ICD further applies therapies to prevent occurrence of further arrhythmias or ventricular fibrillation of the heart of the test subject, wherein model system further comprises a telemetry system for downloading signals and any response applied by the ICD; and a test

analysis system for processing the signals received from the ICD to verify efficacy of any response applied by the ICD to the heart of the non-human test subject. The specification is not enabling for the claimed invention because the disclosure does not provide sufficient guidance and working examples as to how an artisan of skill would have made the claimed invention and the artisan would have required undue experimentation to make the claimed invention as discussed below.

The claimed embodiment comprises a model system comprising a non-human test subject. The claimed embodiment would therefore encompass any non-human species including mouse, pig, and chimpanzee. The claimed embodiment also comprises a non-human test subject wherein the anterior descending portion of the coronary artery of the heart is surgically or chemically blocked, or both. The claimed embodiment would therefore encompass a model system wherein the anterior descending portion of the coronary artery of the heart is surgically blocked, chemically blocked or both surgically and chemically blocked. Whereas the disclosure enables a model system comprising a canine test subject wherein the anterior descending portion of the coronary artery of the heart is surgically blocked, the specification does not enable a skilled artisan to make and use a model system comprising any non-human test subject other than a canine wherein the anterior descending portion of the coronary artery of the heart is surgically blocked, chemically blocked or both surgically and chemically blocked.

At the time of the invention, the state of the art taught animal models of arrythmias and ischaemia in dogs, pigs, rabbits, cats, and rats. However, the art also

taught that there are several significant limitations to the application of the same methodology for making a model system for cardiovascular events in different species. Janse et al. (Card Res 39:165-177, 1998) teach that "a number of (further) processes critical for the electrical changes in acute myocardial ischaemia might be different in rats and guinea pigs from larger species." (page 169, paragraph 2). For example, one of the most important factors that determine whether ventricular fibrillation occurs is the degree of collateral flow and heart rate. Janse et al. teaches, "There is a variation among species in the degree of collateral blood flow following coronary artery occlusion. For example, in rat, rabbit and pig hearts collateral flow is not significantly different from zero, in the guinea pig it is not different from normal control," and in the dog, "there is a variation in pre-existing collaterals, and depending on the degree of collateral flow, the incidence of ventricular fibrillation may vary from zero to 100% after occlusion of a major artery." (page 170, paragraph 3) In terms of ventricular arrythmias, Janse et al. teach that "while there seems an approximate similarity among the electrophysiological changes observed in large animals in certain cases of acute ischaemia in humans, several experimental observations indicate that the arrhythmias observed in small animals (guinea pigs, rats) during acute ischaemia differ from the arrythmias observed in larger species." (page 169, paragraph 1). The authors conclude, "It is clear that species differences do exist with respect to factors that determine arrhythmogenesis . . . " (page 173, paragraph 1) Therefore, because of the unpredictability of cardiovascular models in different animal species and the lack of guidance provided by the specification, a skilled artisan would not have been able to make and use the claimed

invention, a non-human test subject wherein the test subject is any species other than canine.

Further, the state of the art teaches animal model systems of arrythmia and ischaemia wherein the anterior descending portion of the coronary artery of the heart is surgically blocked. For example, Hoffman et al. (J Cardiothorac Vasc Anesth 17(4):495-8, 2003) utilize a balloon occluder to induce coronary artery constriction while Okazaki et al. (Jpn J Thorac Cardiovasc Surg 51(8):349-54, 2003) used bi-directionally stretched elastic sutures during off-pump coronary artery bypass grafting in order to occlude a coronary artery. The state of the art also teaches experimental complete atrioventricular block by surgical, chemical and electrical techniques. For example Weir et al. (Basic Res Cardiol 70(4): 446055, 1975) discussed three methods of AV block, thoracotomy, atriotomy and ligation of the AV bundle. Gonzalez et al. (Am J Physiol 241(2):H283-7, 1981) induced complete AV block with an electrode-catheter technique and Day et al (Am J Physiol 261(4Pt2):H1312-6, 1991) described a technique for producing complete AV block in dogs utilizing formaldehyde injections. However, the art does not teach block of the descending portion of the coronary artery with non-surgical techniques comprising either chemical compositions or chemical compositions in combination with surgical techniques. The instant specification teaches only the induction of atrioventricular block by the surgical ligation of the descending portion of the coronary artery in a canine. However, the claimed invention is directed to the induction of atrioventricular block by surgically blocking, chemically blocking or both surgically and chemically blocking the anterior descending portion of the coronary

artery. Neither the disclosure nor the art provide guidance to enable a skilled artisan to make this claimed embodiment. Therefore, a model system comprising a non-human test subject wherein the anterior descending portion of the coronary artery of the heart is chemically blocked or chemically and surgically blocked to induce an atrioventricular block sufficient for induction of myocardial infarction would be unpredictable in view of the state of the art.

While the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art, an artisan would require specific guidance to carry out the full breadth of the claimed invention.

The instant specification directs to a model system for artificially inducing a heart arrhythmia comprising a non-human test subject having an artificially induced atrioventricular block in the heart, wherein the anterior descending portion of the coronary artery of the heart is surgically or chemically blocked, or both, wherein said non-human test subject has coupled to a myocardial nerve conduction pathway leading to the left ventricle of the heart, means for stimulating myocardial hyperinnervation in the left ventricle comprising an electrical lead for administering an electrical current to the myocardial nerve conduction pathway or an osmotic pump for administering nerve growth factor , wherein non-human test subject further having electrical leads coupled to the heart, means for detecting electrical heart signals represententative of the induced heart arrhythmia comprising an implantable cardioverter-defibrillator (ICD) as a means for pacing the heart in response to the induced heart arrhythmia, wherein the ICD further applies therapies to prevent occurrence of further arrhythmias or ventricular

fibrillation of the heart of the test subject, wherein model system further comprises a telemetry system for downloading signals and any response applied by the ICD; and a test analysis system for processing the signals received from the ICD to verify efficacy of any response applied by the ICD to the heart of the non-human test subject. A working example teaches a model system comprising a canine test subject wherein AV block is induced by the complete ligation of the left anterior descending coronary artery below the first diagonal branch to create an MI. Neither the disclosure nor the art teach a working example of a non-human test subject of any animal species other than canine for use in a model system for artificially inducing a heart arrhythmia. Neither the disclosure nor the art teach a working example of a non-human test subject of any animal species wherein the left anterior descending coronary artery of the heart is chemically blocked. Neither the disclosure nor the art teach a working example of a non-human test subject of any animal species wherein the left anterior descending coronary artery of the heart is both chemically and surgically blocked.

In order for the full breadth of the invention to be enabled, a skilled artisan would have to be able to utilize any non-human test subject in a model system wherein a heart arrhythmia is induced comprising a step wherein the left anterior descending portion of the coronary artery is surgically, chemically or both surgically and chemically blocked. The art does not teach chemical or chemical and surgical block of the coronary artery in any non-human test subject for induction of a heart arrhythmia and the instant specification does not offer guidance or a working example encompassing the full breadth of the invention. It would therefore require an undue quanitity of necessary

experimentation by a skilled artisan to make the claimed invention. For example, in order to make a model system comprising a rat test subject wherein a heart arrhythmia is induced in a rat by chemical blockage of the left anterior descending portion of the coronary artery, a skilled artisan would have to manipulate and alter the components of the model system: electrical leads of the left ventricle, the implantable ICD, the telemetry system, the electric current or osmotic pump for stimulating myocardial hyperinnervation would all have to be modified to fit, and tested to work, in a much smaller cardiovascular system. Additionally, because chemical blockage of the left anterior descending portion of the coronary artery has not been taught in the art or in the instant specification, a skilled artisan would have to identify a chemical compound, optimize a dosage of administration of the compound, and optimize a method of administration of the compound to create an atrioventricular block sufficient to induce an MI. This would represent an undue burden of necessary experimentation by a skilled artisan in light of the state of the art of animal species differences in cardiovascular models and the lack of guidance provided by the specification and the art as discussed previously.

Therefore, in view of the discussion above, the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make the claimed invention commensurate with the full scope of the claims and therefore, limiting the scope of the claimed invention to a model system for artificially inducing a heart arrhythmia consisting of a canine test subject

wherein the anterior descending portion of the coronary artery of the subject is surgically ligated for induction of a myocardial infarction wherein said canine test subject has coupled to a myocardial nerve conduction pathway leading to the left ventricle of the heart, means for stimulating myocardial hyperinnervation in the left ventricle comprising an electrical lead for administering an electrical current to the myocardial nerve conduction pathway or an osmotic pump for administering nerve growth factor, wherein canine test subject further having electrical leads coupled to the heart, means for detecting electrical heart signals represententative of the induced heart arrhythmia comprising an implantable cardioverter-defibrillator (ICD) as a means for pacing the heart in response to the induced heart arrhythmia, wherein the ICD further applies therapies to prevent occurrence of further arrhythmias or ventricular fibrillation of the heart of the test subject, wherein model system further comprises a telemetry system for downloading signals and any response applied by the ICD; and a test analysis system for processing the signals received from the ICD to verify efficacy of any response applied by the ICD to the heart of the canine test subject is proper.

3. Claims 1-9 and 11-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claim(s) 1-9 and 11-21 encompasses a model system for artificially inducing a heart arrhythmia comprising a non-human test subject having an artificially induced atrioventricular block in the heart, wherein the anterior descending portion of the coronary artery of the heart is surgically or chemically blocked, or both. These compositions encompass a diverse group of genera and subgenera and have been defined on the basis of their effect, and not on any specific structure. For example, the claimed embodiment would comprise a non-human test subject that is a pig, rabbit, or monkey. Also, the claimed embodiment would comprise a test subject wherein the anterior descending portion of the coronary artery of the heart is surgically blocked by a surgical procedure, by administration of a chemical compound, or by both a surgical procedure and administration of a chemical compound. The structures of the genera and subgenera are so diverse that the description of one species cannot sufficiently describe all species. The specification discloses a canine test subject wherein the anterior descending portion of the coronary artery of the heart is completely ligated below the first diagonal branch. The specification does not disclose any animal species other than canine that could be used as a test subject. The specification does not disclose any other surgical procedures by which the artery could be blocked. The specification does not disclose any chemical compounds that could be administered to block the artery. What would be the structure of such a chemical compound? The specification does not disclose the combination of surgical procedure with chemical compound administration that could be used to block the artery. Therefore, while the specification teaches one surgical method to block the coronary artery in a canine test

subject; this is not representative of the genera and subgenera of the claimed embodiment.

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the claimed embodiment is directed to a non-human test subject wherein the anterior descending portion of the coronary artery of the heart is surgically blocked, chemically blocked or both surgically and chemically blocked. The working example describes a canine test subject wherein "the left anterior descending coronary artery of the heart is completely ligated below the first diagonal branch." The possession of a canine test subject wherein the coronary artery of the heart is completely ligated cannot predict the complete structure and specific characteristics of a chemically blocked artery or a coronary artery that is blocked using wires or a catheter, for example. The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics that would distinguish different members of the claimed genus would be a measurable change in the function of the coronary artery such as blood flow or arterial pressure. The specification does not disclose the characteristics of these functions. For example, there is no discussion in the

specification as to the blood flow level or arterial pressure required to be attained in order for an MI or AV block to occur. Therefore, because such functional characteristics are not disclosed, one of skill in the art could not distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of a model system comprising a non-human test subject of any animal species other than canine wherein the anterior descending portion of the coronary artery of the subject is blocked by any surgical procedure other than complete ligation below the first diagonal branch, any chemical procedure or by a combination of surgical and chemical procedure, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1 is directed to a model system for artificially inducing a heart arrhythmia, comprising a non-human test subject having an artificially induced atrioventricular block.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because the metes and bounds of the term "atrioventricular block" is not clear.

Conclusion

5. No claims are allowed.

6. Amendment filed with a Request for Continued Examination on 5/11/04 has been entered.

7. Applicant's amendment to claims 1-9 and 11-21 is acknowledged. However, this amendment does not obviate the rejections set forth in the previous office actions on 8/26/03 and 2/18/04, because the claim writes the limitation "comprising."

8. The 112 second paragraph rejection made for claims 6-7, 13-14, and 18-19 have been withdrawn in view of the applicant amendment on 5/11/04.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

NCA

RAM R. [illegible] PH.D.
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